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Title: THERAPEUTIC AND DIAGNOSTIC COMPOUNDS, COMPOSITIONS, AND METHODS

IN THE CLAIMS

Please amend the claims as follows:

- 1. (Original) A complex comprising:
 - a) compound of formula (I):

$$R_1$$
 N — $(CH_2)_n$
 R_1
 R_1
 $(CH_2)_n$ — N
 R_1
 (I)

wherein:

each R₁ is independently hydrogen or (C₁-C₄)alkyl, optionally substituted with

carboxy;

each X is independently $(CH_2)_n$ or

and each n is independently 2, 3, or 4;

wherein the compound of formula I is substituted on one or more carbons other than a carbon of R_1 with one or more groups $-Y(PO_3H_2)_m$; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof; and

- b) a detectable or therapeutic radionuclide.
- 2. (Original) The complex of claim 1 wherein each R_1 is independently (C_1 - C_4)alkyl, substituted with carboxy.

3. (Original) The complex of claim 1 wherein each R₁ is carboxymethyl or 2-carboxyethyl.

- 4. (Original) The complex of claim 1 wherein each R_1 is carboxymethyl.
- 5. (Original) The complex of claim 1 wherein each n is independently 2 or 3.
- 6. (Original) The complex of claim 1 wherein each n is 2.
- 7. (Original) The complex of claim 1 wherein the linker group Y is about 5 angstroms to about 100 angstroms in length.
- 8. (Original) The complex of claim 1 wherein the linker group Y is about 10 angstroms to about 50 angstroms in length.
- 9. (Original) The complex of claim 1 wherein the compound of formula I is substituted on a carbon other than a carbon of R_1 with one or two groups $-Y(PO_3H_2)_m$, wherein m is 1, 2, 3, 4, 5, or 6.
- 10. (Original) The complex of claim 1 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C_1-C_{10}) alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1-C_4) alkyl.
- 11. (Original) The complex of claim 10 wherein the linker group Y is an amino acid.
- 12. (Original) The complex of claim 11 wherein the amino acid is non-lipophilic.
- 13. (Original) The complex of claim 10 wherein the linker group Y is a saccharide.

- 14. (Original) The complex of claim 13 wherein the saccharide is a monosaccharide, disaccharide, or trisaccharide.
- 15. (Original) The complex of claim 13 wherein the saccharide is a polysaccharide.
- 16. (Original) The complex of claim 10 wherein the linker group Y is a peptide.
- 17. (Original) The complex of claim 16 wherein the peptide comprises 2 to 25 amino acid residues.
- 18. (Original) The complex of claim 17 wherein the amino acid residues are non-lipophilic.
- 19. (Original) The complex of claim 10 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 20. (Original) The complex of claim 10 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 21. (Original) The complex of claim 10 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 22. (Original) The complex of claim 10 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within

the chain or at the terminus of the chain, which chain is substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1-C_4) alkyl.

23. (Original) The complex of claim 1 wherein each -Y(PO₃H₂)_m is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-(II)

phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino}-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino}-benzyl; or 4-[4-(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl.

24. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula (II):

$$R_1$$
 $N-(CH_2)_n$
 R_1
 R_1
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 $(CH_2)_n$

wherein:

each R_1 is independently hydrogen or (C_1-C_4) alkyl, optionally substituted with carboxy (COOH); and each n is independently 2, 3, or 4; wherein the compound of formula (II) is substituted on one or more carbons other than a carbon of R_1 with one or more groups -

 $Y(PO_3H_2)_m$; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

- 25. (Original) The complex of claim 24 wherein each R_1 is independently (C_1 - C_4)alkyl, substituted with carboxy.
- 26. (Original) The complex of claim 24 wherein each R₁ is carboxymethyl.
- 27. (Original) The complex of claim 24 wherein the compound of formula II is substituted on a carbon other than a carbon of R_1 with one or two groups $-Y(PO_3H_2)_m$.
- 28. (Original) The complex of claim 24 wherein the compound of formula II is substituted on carbon with one group $-Y(PO_3H_2)_m$.
- 29. (Original) The complex of claim 24 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C_1-C_{10}) alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1-C_4) alkyl.
- 30. (Original) The complex of claim 24 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 31. (Original) The complex of claim 24 wherein each -Y(PO₃H₂)_m is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-

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acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino}-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino}-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl; or 4-[4-(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl.

32. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula III:

$$\begin{array}{c|c}
R_1 & R \\
N & N
\end{array}$$

$$R_1 & R_1$$
(III)

wherein:

each R_1 is independently hydrogen or (C_1-C_4) alkyl, optionally substituted with carboxy (COOH); and wherein the compound of formula III is substituted on one or more carbons other than a carbon of R_1 with one or more groups $-Y(PO_3H_2)_m$; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

- 33. (Original) The complex of claim 32 wherein each R_1 is independently (C_1 - C_4)alkyl, substituted with carboxy.
- 34. (Original) The complex of claim 32 wherein each R₁ is carboxymethyl.
- 35. (Original) The complex of claim 32 wherein the compound of formula III is substituted with one or two groups $-Y(PO_3H_2)_m$.
- 36. (Original) The complex of claim 32 wherein the compound of formula III is substituted with one group $-Y(PO_3H_2)_m$.

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- 37. (Original) The complex of claim 32 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C_1-C_{10}) alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1-C_4) alkyl.
- 38. (Original) The complex of claim 32 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 39. (Original) The complex of claim 32 wherein each -Y(PO₃H₂)_m is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino}-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino}-benzyl; or 4-[4-(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl.
- 40. (Original) The complex of claim 32 wherein each R_1 is independently (C_1-C_4) alkyl, substituted with carboxy (COOH); and wherein the ring is substituted on carbon with a group $Y(PO_3H_2)_m$; or a pharmaceutically acceptable salt thereof.

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41. (Original) The complex of claim 1 wherein the compound of formula I is a compound of formula IV:

$$R_1$$
 N
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 R_1
 $(CH_2)_n$
 $(CH$

wherein:

each R_1 is independently hydrogen or $(C_1\text{-}C_4)$ alkyl, optionally substituted with carboxy (COOH); and each n is independently 2, 3, or 4; wherein the compound of formula IV is substituted on one or more carbons other than a carbon of R_1 with one or more groups - $Y(PO_3H_2)_m$; wherein Y is a linker group; and m is 1, 2, 3, 4, 5, or 6; or a pharmaceutically acceptable salt thereof.

- 42. (Original) The complex of claim 41 wherein each R_1 is independently (C_1 - C_4)alkyl, substituted with carboxy.
- 43. (Original) The complex of claim 41 wherein each R_1 is carboxymethyl.
- 44. (Original) The complex of claim 41 wherein the compound of formula IV is substituted with one or two groups $-Y(PO_3H_2)_m$.
- 45. (Original) The complex of claim 41 wherein the compound of formula IV is substituted with one group $-Y(PO_3H_2)_m$.
- 46. (Original) The complex of claim 41 wherein the linker group Y is an amino acid, a peptide, a saccharide, or a divalent (C_1-C_{10}) alkyl chain, optionally comprising one or more non-

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peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.

- 47. (Original) The complex of claim 41 wherein the linker group Y is a divalent (C_1 - C_{10})alkyl chain, optionally comprising one or more non-peroxide oxy (-O-), -N(R_d)-, or divalent aryl within the chain or at the terminus of the chain, which chain is optionally substituted on carbon with one or more oxo (=O), thioxo (=S), or hydroxy, wherein R_d is hydrogen or (C_1 - C_4)alkyl.
- 48. (Original) The complex of claim 41 wherein each -Y(PO₃H₂)_m is independently 4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl; 4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl; 4-(3,3-Bis-phosphono-propionylamino)-benzyl; 4-[4-(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-butyrylamino]-benzyl; 4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-acetylamino]-methyl}-propionylamino)-benzyl; 4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-[propionylamino}-benzyl; 4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propionylamino)]-methyl]-carbamoyl}-butyrylamino)-benzyl; 4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl; or 4-[4-(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl.
- 49. (Original) The complex of claim 1 wherein the compound of formula I is (6-{4-[2-(Bis-phosphonomethyl-amino)-acetylamino]-benzyl}-4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid; (6-{4-[4-(Bis-phosphonomethyl-carbamoyl)-butyrylamino]-benzyl}-4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid; {3-[4-(3,3-Bis-phosphono-propionylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl}-acetic acid;

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- (4,7,10-Tris-carboxymethyl-3-{4-[4-(3-hydroxy-3,3-bis-phosphonopropyl-carbamoyl)-butyrylamino]-benzyl}-1,4,7,10-tetraaza-cyclododec-1-yl)-acetic acid;
- {3-[4-(3-[2-(Bis-phosphonomethyl-amino)-acetylamino]-2-{[2-(bis-phosphonomethyl-amino)-acetylamino]-methyl}-propionylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl}-acetic acid;
- {6-[4-(4-{Bis-[(bis-phosphonomethyl-carbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl}-acetic acid;
- [3-(4-{3-(3,3-Bis-phosphono-propionylamino)-2-[(3,3-bis-phosphono-propionylamino)-methyl]-propionylamino}-benzyl)-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl]-acetic acid;
- {6-[4-(4-{Bis-[(3-hydroxy-3,3-bis-phosphono-propylcarbamoyl)-methyl]-carbamoyl}-butyrylamino)-benzyl]-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl}-acetic acid; [6-(4-{4-[(Bis-phosphono-methyl)-carbamoyl]-butyrylamino}-benzyl)-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl]-acetic acid; or (6-{4-[4[(Bis-{[(bis-phosphono-methyl)-carbamoyl]-methyl}-carbamoyl)-butyrylamino]-benzyl}-4,7,10-tris-carboxymethyl-1,4,7,10tetraaza-cyclododec-1-yl)-acetic acid.
- 50. (Original) The complex of claim 1 which comprises a detectable radionuclide.
- 51. (Original) The complex of claim 50 wherein the detectable radionuclide is Technetium-99m, Ruthenium-97, Indium-111, Gallium-67 or -68, or Lead-203.
- 52. (Original) The complex of claim 1 which comprises a therapeutic radionuclide.
- 53. (Original) The complex of claim 52 wherein the therapeutic radionuclide is Holmium-166, Yttrium-90, Samarium-153, or Gadolinium-159.
- 54. (Original) The complex of claim 52 wherein the therapeutic radionuclide is Holmium-166.

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55. (Original) A method for detecting the presence or absence of a calcified tissue target site within a mammal, comprising:

administering to the mammal a detectable dose of a complex of claim 50; and detecting the compound in the mammal to determine the presence or absence of the target site.

- 56. (Original) A therapeutic method for suppressing bone marrow in a mammal in need of such therapy comprising administering to the mammal, an effective bone marrow suppressing amount of a complex of claim 52.
- 57. (Original) A therapeutic method for treating cancer in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.
- 58. (Original) A therapeutic method for treating bone pain in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.
- 59. (Cancelled)
- 60. (Currently amended) The A therapeutic method of claim 59 wherein the bone related disease is an immunological disorder, a metabolic disease, an infection, an infectious disease, an inflammatory disease, a hematopoietic disorder, or for treating a condition treatable with stem cell transplantation, with or without gene therapy, that utilize utilizes bone marrow ablation, in a mammal in need of such therapy comprising administering to the mammal an effective amount of a complex of claim 52.
- 61. (Currently amended) The A therapeutic method of claim 59 wherein the disease is for treating Crohn's disease, rheumatoid arthritis, multiple sclerosis, osteoporosis, osteopenia, osteomyelitis, Paget's disease, sickle cell anemia, or a lysosomal or peroxisomal storage disease, in a mammal in need of such therapy comprising administering to the mammal an effective amount of a complex of claim 52.

AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.111

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62. (Original) A pharmaceutical composition comprising the complex of claim 1 and a pharmaceutically acceptable carrier.

63. (New) A therapeutic method for treating an infection in a mammal in need of such therapy comprising administering to the mammal, an effective amount of a complex of claim 52.